REMARKS

Prior to entry of the present amendment, claims 1, 2, 5-10, 13, and 14 are pending. Claims 1, 2, and 5-10 are rejected under 35 U.S.C. § 112, first paragraph, and claims 1, 2, 5-10, 13, and 14 are rejected under 35 U.S.C. § 103. Figure 16 is objected to. Applicants address each basis for rejection or objection as follows.

Claim amendments

New claims 58-60 have been added. Support for new claim 58 is found, for example, in original claims 1 and 2 and at page 60, lines 26-31, of the application published as WO 2005/116076. New claim 59 finds support, for example, in original claim 5. New claim 60 finds support, for example, at page 26, line 28, to page 27, line 1, of the WO 2005/116076 publication. No new matter has been added by the present amendment.

Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

Objection to the drawings

The drawings are objected to because Figure 16 is not labeled. Applicants, herewith, submit a Replacement Sheet for the drawing sheet containing Figure 16 in which this figure is labeled. No new matter is contained in the Replacement Sheet. This basis for objection may be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 2, and 5-10 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Office states (page 3):

> [T]he claims read on a polypeptide that does not include all 6 CDRs.
>
> * * *
>
> The specification does not disclose that a PAM-1 antibody that does not

> include all 6 CDRs was effective in inhibiting tumor growth. The specification also does not disclose any other polypeptide besides an antibody that treats a proliferative disorder.

Applicants respectfully traverse this basis for rejection.

Applicants direct the Office's attention to Example 2 of the enclosed presentation by U.S. Patent and Trademark Office Examiners Yvonne Eyler and Larry Helms entitled "Patenting Antibodies." In particular, in Example 2, the following claims are presented:

> Claim 1. An isolated antibody that binds to human antigen X, said antibody comprises a heavy chain variable domain comprising SEQ ID NO:1.
>
> Claim 2. An isolated antibody that binds to human antigen X, said antibody comprises a light chain variable domain comprising SEQ ID NO:2.

The Example further states:

> The instant specification produced an antibody that binds antigen X that contains a VH of SEQ ID NO:1 and a VL of SEQ ID NO:2, as well as explicitly disclosing humanized and chimeric antibodies.
>
> The instant specification provides examples of detection of cancer in human subjects with an antibody that binds antigen X.

And the Example in the presentation notes that there are several prior art references (from 1991 and 1993) that teach methods of producing antibodies that bind a specific antigen by using a specific VL (or VH) and screening a library of complimentary variable domains. In finding sufficient enablement for claims 1 and 2, the Example concludes (emphasis original):

> In light of the prior art disclosing methods of obtaining antibodies that bind an antigen by screening complementary variable domain libraries, <u>the specification's disclosure of an antibody that binds a specific antigen comprising a defined VH or VL sequence would provide enough structure for one skilled in the art to practice the invention</u>.

Applicants submit, as explained below, that the facts of the present case fall squarely within the situation outlined in the above Example of the U.S.P.T.O. presentation and,

therefore, the present claims should also be found to be enabled by the specification in view of the state of the art at the time of filing.

Claim 1 and its dependent claims require the isolated polypeptide to include at least the sequence of amino acids 28-32, 51-53, and 90-100 of SEQ ID NO:29 (the 3 CDR sequences of the variable light chain). Claim 1 also requires the polypeptide to specifically bind to neoplastic cells or cells of a pre-cancerous lesion but not to a normal cell. Claim 2 depends from claim 1 and requires the polypeptide to further include amino acids 11-18, 36-43, and 82-104 of SEQ ID NO:28 (the 3 CDR sequences of the variable heavy chain). The specification teaches that an antibody containing the sequences of SEQ ID NOS:28 and 29 has the binding specificity required by the claims (see, for instance, Tables 1A and 1B at pages 62 and 63 of the specification).

The specification provides the sequence of the variable light and heavy chains of an antibody having the binding properties required by the claims. Consistent with the analysis provided in the U.S.P.T.O.'s presentation, the specification discloses an antibody with the claimed specific binding characteristics, the claims require the polypeptide to contain at least the 3 CDRs of the variable light chain and, as noted in the U.S.P.T.O presentation, screening complementary variable domain libraries for antibodies that have the same binding characteristics was standard in the art at the time of filing. Applicants submit that the claims provide sufficient structure for one skilled in the art to make and use the invention within the full scope of the claims. This basis for rejection may be withdrawn.

With respect to claim 2, Applicants note that this claim requires the polypeptide to include the three CDR sequences of both the variable heavy and light chain sequences of the PAM-1 antibody described in the specification. As such, the polypeptide of claim 2 contains all 6 CDRs of the PAM-1 antibody. The Office states (page 5):

> A polypeptide does not necessarily comprise the required conformation having the proper antigen binding site of an antibody, and thus does not necessarily bind a neoplastic cell.

Applicants note that the specification describes how to modify a polypeptide sequence to obtain variants that retain the binding specificity of the PAM-1 antibody (see, e.g., page 28, line 8, to page 29, line 23, of the WO 2005/116076 publication). Such modified polypeptides may be tested in the binding assays described in the Examples to identify variants that retain the binding properties of the original PAM-1 antibody. Altering polypeptide sequences and screening for polypeptides with particular binding properties was well within the skill of a molecular biologist at the time of filing. Applicants submit that it would not require undue experimentation to make and use the polypeptides encompassed by claim 2. For this reason as well, the enablement rejection of claim 2 should be withdrawn.

Applicants further submit that new claim 58, which is directed to an antibody containing the six CDR sequences of the PAM-1 antibody, is also free of this basis for rejection.

Rejection under 35 U.S.C. § 103

Claims 1, 2, 5-10, 13, and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Vollmer et al. (Cancer 74:1525-1532, 1994; "Vollmers"), as evidenced by Brändlein et al. (Human Antibodies 11:107-119, 2002; "Brändlein"), in view of Robinson et al. (U.S. Patent No. 5,618,920; "Robinson"). Applicants, for the reasons explained below, submit that this basis for rejection should be withdrawn.

The Office acknowledges that Vollmers does not disclose the sequences recited in the present claims and cites Robinson as teaching methods of determining antibody sequences (page 7 of the Office Action). In asserting that the claimed invention is obvious, the Office states (page 7):

> It would have been prima facie obvious to combine [the] Vollmers et al. PAM-1 antibody with Robinson et al.'s method [of] determination of nucleic acid molecules comprising VH and VL of an antibody to make nucleic acid molecules comprising SEQ ID NOs: 26 and 27 and an antibody

comprising the amino acid sequences of SEQ ID NO:28 and 29.

Applicants respectfully disagree.

While Vollmers (and Brändlein) describe the PAM-1 antibody (originally designated 103/51), these references fail to provide sufficient information for one skilled in the art to make and use this particular antibody, even if the disclosures were to be combined with Robinson. The Vollmers and Brändlein references merely describe methodology involved in isolating the antibody. In particular spleen cells from patients with stomach carcinoma were fused with the heteromyeloma HAB-1, and hybridomas were then screened for antibody production. Following this procedure there are potentially millions of different antibodies that could be produced – the likelihood of isolating a cell line producing exactly the same antibody as PAM-1, and therefore having the sequences required by the claims, is extremely low. In the absence of possession of the cell line producing the PAM-1 antibody, Applicants submit that the teaching of the Vollmers and Brändlein references would not enable one skilled in the art to make the PAM-1 antibody with a reasonable expectation of success even if the techniques of Robinson were used.

Further, with respect to claim 5, Applicants note that this claim requires the polypeptide to be capable of inducing apoptosis of the neoplastic cell or cell of the pre-cancerous lesion, but not of a normal cell. The Office states (page 7):

> Neither Vollmers et al. nor Robinson et al. disclose an antibody that induces apoptosis. However, the antibody of Vollmers et al. and Robinson et al. would inherently induce apoptosis. The rejection based on inherency is based on the property that the PAM-1 antibody induces apoptosis of tumor cells.

Applicants respectfully disagree with the Office's characterization of the PAM-1 antibody disclosed in the cited art.

Of the cited references, as stated above, only Vollmers and Brändlein describe the PAM-1 antibody. Neither of these references, however, describes a PAM-1 antibody that

induces *apoptosis*. On the contrary, the PAM-1 antibody described in Vollmers and Brändlein induces *proliferation* of tumor cells. Applicants direct the Office's attention to Figure 3 of Vollmers, where Vollmers shows that the intact PAM-1 antibody (antibody 103/51) stimulates proliferation of two stomach carcinoma cell lines. Vollmers goes on to state (page 1531, left column):

> How the monoclonal antibodies 103/51 and 105/79 induce their enhancing effects is not known. They might mimic the binding of a growth factor to tumor cells ... or bind to an unknown cell surface receptor and produce a direct stimulating effect.

Clearly, the PAM-1 antibody described by Vollmers does not inherently induce apoptosis of a tumor cell.

It was Applicants who discovered that a fragmented or recombinant PAM-1 antibody induces apoptosis. As described in the specification, for instance, in Example 4, cleavage of the pentameric PAM-1 antibody into monomeric antibodies resulted in antibodies that induced apoptosis of stomach carcinoma cells *in vitro* and *in vivo* in a mouse tumor growth model. This property of a fragmented PAM-1 antibody is not taught or suggested by the cited art, even if combined, and is reflected in claim 5 which requires that the binding of the polypeptide to the cell results in apoptosis of the neoplastic cell or cell of a pre-cancerous lesion. The cited art fails to teach or suggest all of the elements required by this claim. Hence, Applicants submit that the cited art, even if combined, cannot render claim 5 obvious. For this reason as well, the rejection of claim 5 under 35 U.S.C. § 103 should be withdrawn.

Applicants also submit that new claim 59 is free of the present obviousness rejection because it too requires the antibody to induce apoptosis of the neoplastic cell or cell of a pre-cancerous lesion to which it specifically binds.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three (3) months, to and including September 20, 2010, because September 18th falls on a Saturday, and an authorization to charge the required extension fee to Deposit Account No. 03-2095.

Also enclosed is an authorization to charge $110.00 to Deposit Account No. 03-2095 in payment of excess claims fees for one independent claim in excess of three.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 17, 2010

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Patenting Antibodies

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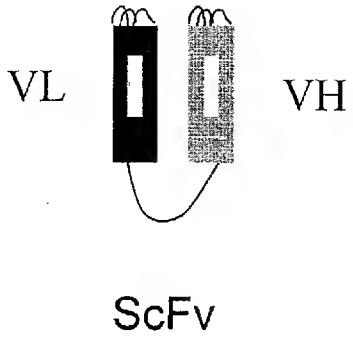
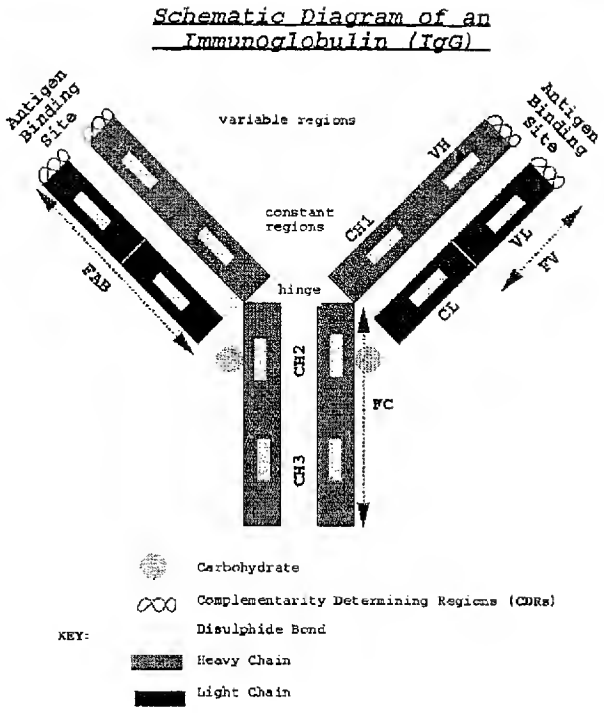
Antibody Structure

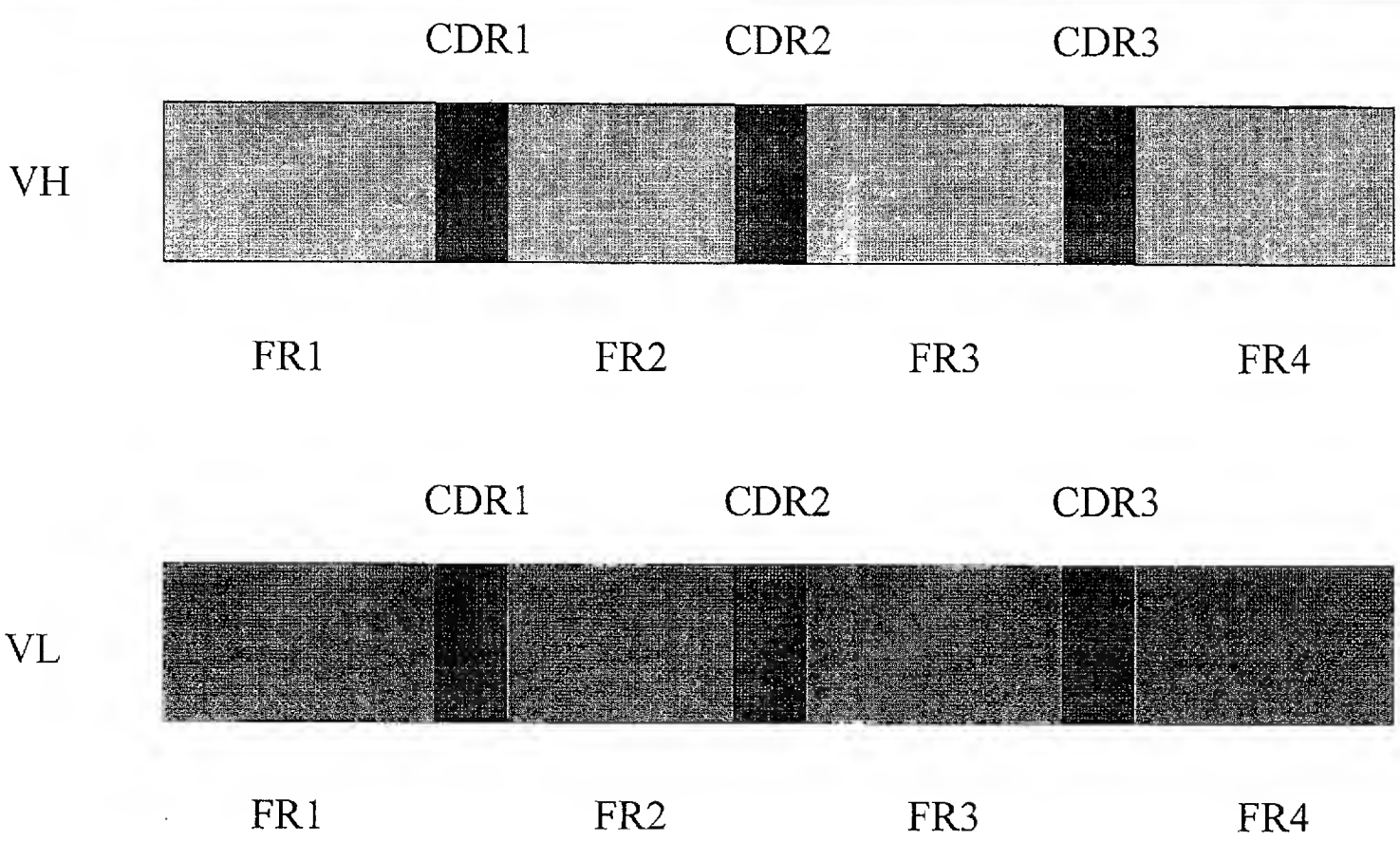


ScFv

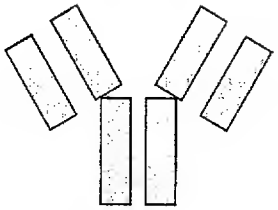


Adapted from people.cryst.bbk.ac.uk/~ubcg07s/gifs/igG.gif

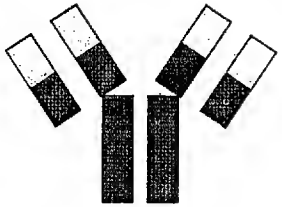
Variable domain of Antibodies



Humanization of Antibodies



Mouse

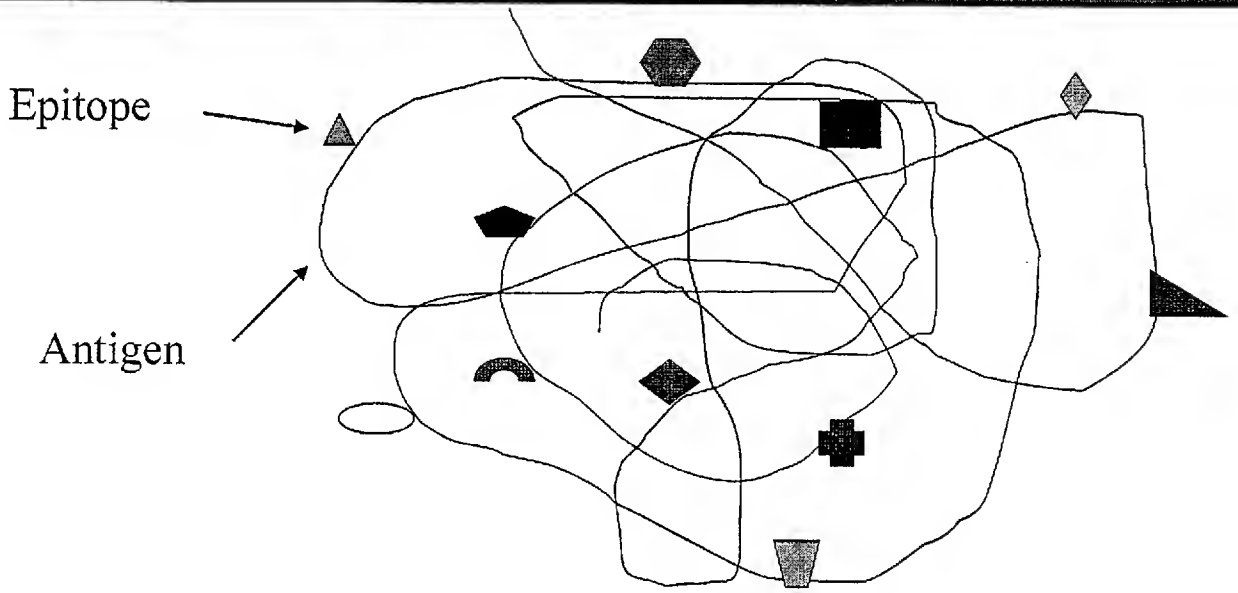


Chimaeric

Humanized

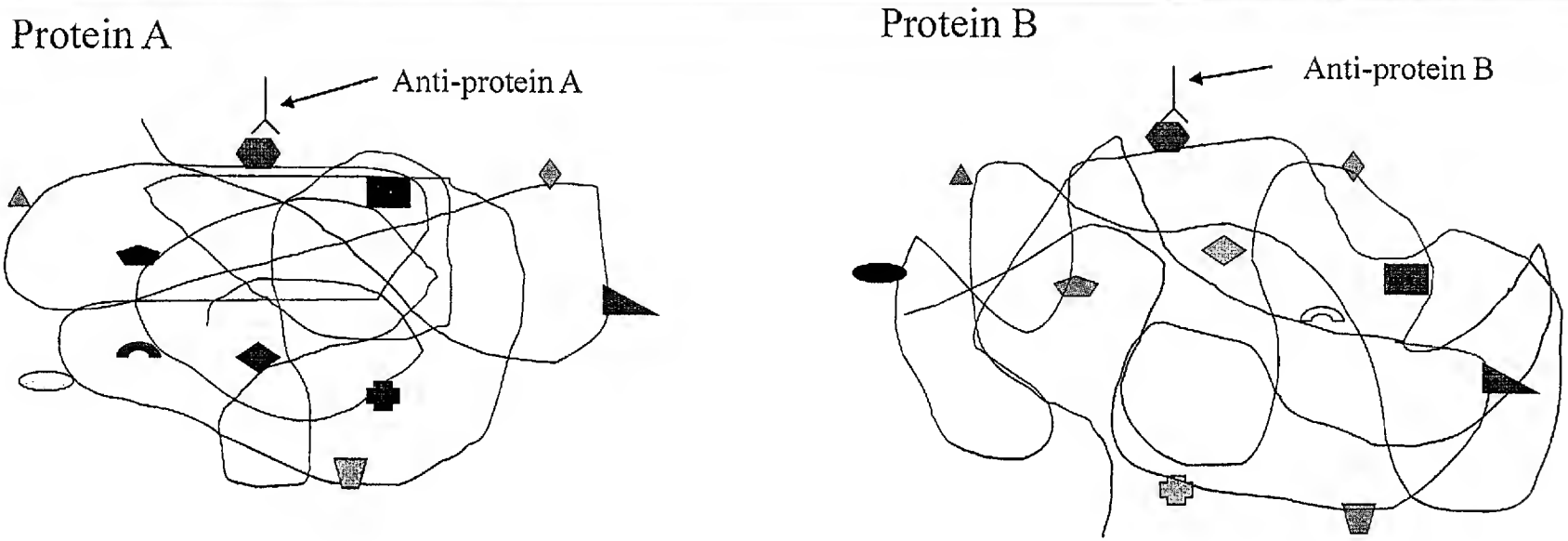
Human

Epitopes



The actual portions or fragments of an antigen that react with receptors on B-lymphocytes and T-lymphocytes, as well as free antibody molecules, are called epitopes or antigenic determinants. The size of an epitope is generally thought to be equivalent to 5-15 amino acids or 3-4 sugar residues.

Epitopes cont.



Cross-reacting antibody: An antibody that reacts with epitopes on an antigen molecule differing from the one that stimulated its synthesis. The effect is attributable to shared epitopes on the two antigen molecules.

Cruse et al., *Illustrated Dictionary of Immunology,* CRC Press, New York, 1995

Epitopes cont.

• Specificity:

1). Recognition by an antibody of a specific epitope in the presence of other epitopes.
Cruse et al., *Illustrated Dictionary of Immunology,* CRC Press, New York, 1995

2). Property of antibodies which enable them to react with some antigenic determinants and not with others.
Medical dictionary: Antibody specificity-WrongDiagnosis.com

3). The specificity of an antibody is its ability to discriminate between two different epitopes.
From http://users.rcn.com/kimball.ma.ultranet/BiologyPages/A/Affinity.html

It is acknowledged in the art that an antibody can bind to any epitope that has the correct conformation, and this potentially includes the protein used for immunization, as well as any protein with a similar epitope. (Burry, J. *Histochem Cytochem* **48**:163-165, 2000)

Written Description

The effect of recent decisions on examination

Written Description

35 USC § 112

The specification shall contain a ***written description*** of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Example 1

- Claim 1. A monoclonal antibody that specifically binds Protein X.
- Claim 2. The antibody of claim 1 which binds murine Protein X.
- Claim 3. The antibody of claim 1 which binds human Protein X.

This example is based on the fact pattern in *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004).

Specification

- The specification describes a monoclonal antibody that specifically binds to Protein X isolated from murine tissue.
- The specification explains that an antibody that specifically binds Protein X can be used to repress cell-to-cell signaling interactions between certain cells in the immune system.
- The specification discloses several physical and chemical properties of isolated murine Protein X including the amino acid sequence.
- The specification does not disclose a physical or chemical property for Protein X from another species, however, the specification discloses that human Protein X is expected to have the same *in vivo* function as murine Protein X.

Analysis

- Claim 2: The specification characterizes murine Protein X sufficiently so that those of skill in the art would accept that applicant had possession of murine Protein X at the time the application was filed.
- The level of skill and knowledge in the art of antibodies at the time of the filing was such that production of antibodies against a well-characterized antigen was conventional and those of skill in the art of immunology would accept that an adequate description of a purified antigen would put an inventor in possession of antibodies that bind the purified antigen.
- Accordingly, there is adequate written description support for claim 2.

Analysis (cont.)

- Claims 1 and 3: The specification does not describe actual reduction to practice of an antibody that binds human Protein X or Protein X from any non-murine source.
- The specification does not describe the complete structure of an antibody that binds Human Protein X or Protein X from a non-murine source.
- The specification does not disclose a correlation between human Protein X or Protein X from other species and the structure of the claimed antibody.
- The specification does not describe a method of making an antibody that binds human Protein X or Protein X from other sources that can be done without the specific Protein X.

Analysis (cont.)

- A review of the specification as well as the prior art finds no evidence that the disclosed properties of murine Protein X are predictive of corresponding properties for human Protein X.
- The description of Protein X is simply functional and there is no evidence that those of skill in the art would accept a disclosure of murine Protein X and its antibodies as evidence that the inventor had possession of human Protein X.
- Claim 3 is directed to an unknown identified by reference to another unknown.
- Claim 1 is directed to a genus that is not adequately described.

Conclusion of Analysis

- Claim 2 is supported by an adequate written description.
- Claims 1 and 3 are not supported by an adequate written description.
- Claims 1 and 3 should be rejected for lack of written description support.

Summary of Holdings in Noelle

- "Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen." *Noelle*, 355 F.3d at 1349 (Fed. Cir. 2004) (emphasis in original).

Example 2

- Claim: A monoclonal antibody that binds to human X antigen.

- This example is adapted from part of the fact pattern in *Chiron Corp. v. Genentech, Inc.* , 363 F.3d 1247 (Fed. Cir. 2004).

The Specification

- Disclosed antigen X from human tissue.
- Disclosed the term "monoclonal antibody" means an antibody composition having a homogeneous antibody population. It is not intended to be limited as to the source of the antibody or the manner in which it is made.
- The instant application claims the benefit of an earlier filed application (parent) and the parent does not mention humanized or chimaeric antibodies or an explanation of the term "monoclonal antibody".
- The instant application explicitly discloses humanized and chimaeric antibodies.

Prior Art

- An intervening prior art reference published after the filing date of the parent application, but before the actual filing date of the present application, discloses humanized and chimaeric antibodies to human antigen X.

Analysis

- In the light of specification's disclosure, the term "monoclonal antibody" is given the broadest reasonable interpretation and includes homogeneous antibody populations made by any technology.
- Thus, the claim includes antibodies obtained from hybridomas as well as from engineering technology, including humanized or chimaeric antibodies.

Analysis (cont.)

- Chimaeric and humanized antibodies were added to the disclosure of the parent when the present application was filed.
- A review of the relevant prior art shows that chimaeric antibody technology did not exist at the time the parent application was filed.
- Accordingly, the present claim is not entitled to the filing date of the parent application and gets the filing date of the present application.
- Therefore, the claim must be rejected as anticipated by the intervening reference.

Summary of Holdings in Chiron

- Because chimeric antibody technology did not even exist at the time of the 1984 filing, the record conclusively supports that the Chiron scientists did not possess and disclose this technology in the February 1984 filing. See *Union Oil Co. of Cal. v. Atl. Richfield Co.*, 208 F.3d 989, 998 (Fed. Cir. 2000) (A jury determined "that, as of the filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter of the claims."). Thus, the '561 patent cannot claim priority based on the 1984 application because it fails to comply with the written description requirement. The written description requirement prevents applicants from using the amendment process to update their disclosures (claims or specifications) during their pendency before the patent office. Otherwise applicants could add new matter to their disclosures and date them back to their original filing date, thus defeating an accurate accounting of the priority of invention. See 35 U.S.C. § 132. The law does not expect an applicant to disclose knowledge invented or developed after the filing date. Such disclosure would be impossible. See In re Hogan, 559 F.2d 595, 605-06 (CCPA 1977)." from *Chiron Corp. v. Genentech, Inc.* , 363 F.3d 1247 (Fed. Cir. 2004).

Enablement

35 USC § 112

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

MPEP 2164.01(a) Undue Experimentation Factors (*In re Wands*):

(1) The breadth of the claims

(2) The nature of the invention

(3) The state of the prior art

(4) The level of one of ordinary skill

(5) The level of predictability in the art

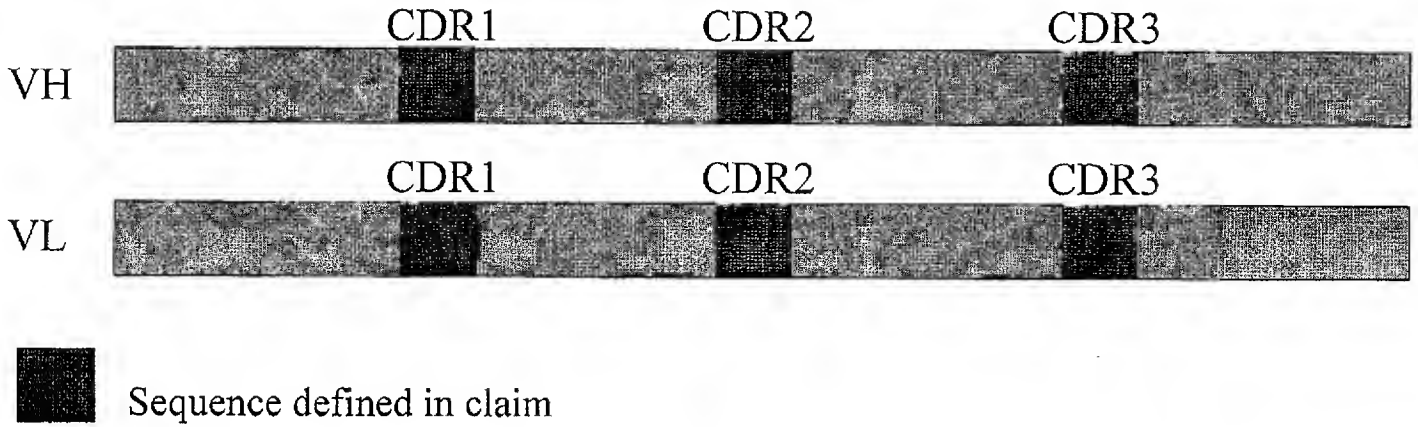
(6) The amount of direction provided by the inventor

(7) The existence of working examples

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Example 1

- Claim: An isolated antibody that binds to human antigen X, said antibody comprises a heavy chain variable domain comprising the 3 CDRs in SEQ ID NO:1 and a light chain variable domain comprising the 3 CDRs in SEQ ID NO:2.



Specification

- Discloses antigen X from human tissue.
- Discloses antigen X is over-expressed in cancer tissue vs. normal tissue.
- The instant application produced an antibody that binds antigen X that contains a VH of SEQ ID NO:1 and a VL of SEQ ID NO:2, as well as explicitly disclosing humanized and chimaeric antibodies.
- The instant application provides examples of detection of cancer in human subjects with an antibody that binds antigen X.

State of the Prior Art

- It was well known at the time the application was filed that the heavy and light polypeptide chains each contribute three CDRs to the antigen binding region of the antibody molecule.
- The prior art[1] taught humanization of antibodies by transfer of the 6 CDRs from a donor framework region to an acceptor framework region and retention of antigen binding.

[1]Queen et al., PNAS (1988) 86:10029-10033,
Riechmann et al., Nature (1988) 332:323-327

Analysis

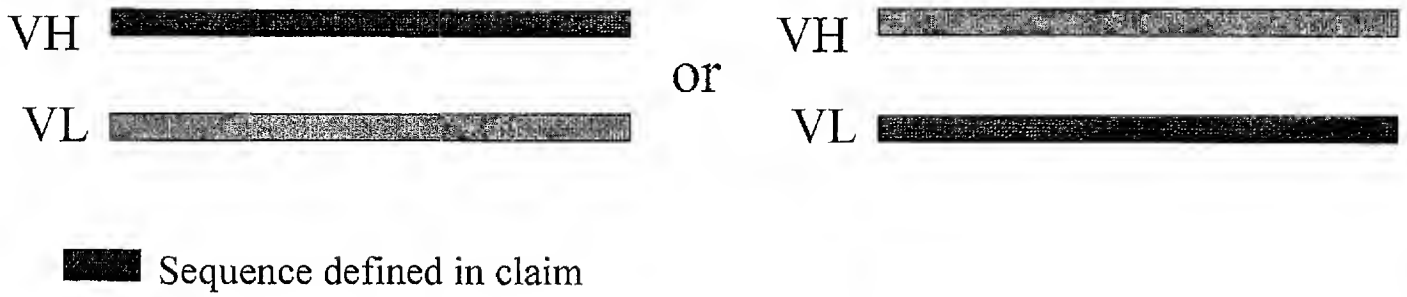
- In light of the prior art disclosing the CDRs as being the essential structure of the antibody's binding site, the identification of the specific CDR sequences in the specification provides enough structure to define the antibody's binding site.
- In addition, the prior art for humanization supports obtaining successful antigen binding by transferring the 6 CDRs from a donor framework to an acceptor framework.

Analysis (cont.)

- Thus, it would not have been undue experimentation to obtain an antibody that would bind antigen X and comprise the 6 CDRs as specifically defined in the claim at the time of filing.
- Therefore, a claim that defines an antibody that binds antigen X and comprises a heavy chain variable region comprising the 3 CDRs in SEQ ID NO:1 and a light chain variable region comprising the 3 CDRs in SEQ ID NO:2 meets the requirements under 35 U.S.C. 112, first paragraph, for enablement.

Example 2

- Claim 1. An isolated antibody that binds to human antigen X, said antibody comprises a heavy chain variable domain comprising SEQ ID NO:1.
- Claim 2. An isolated antibody that binds to human antigen X, said antibody comprises a light chain variable domain comprising SEQ ID NO:2.

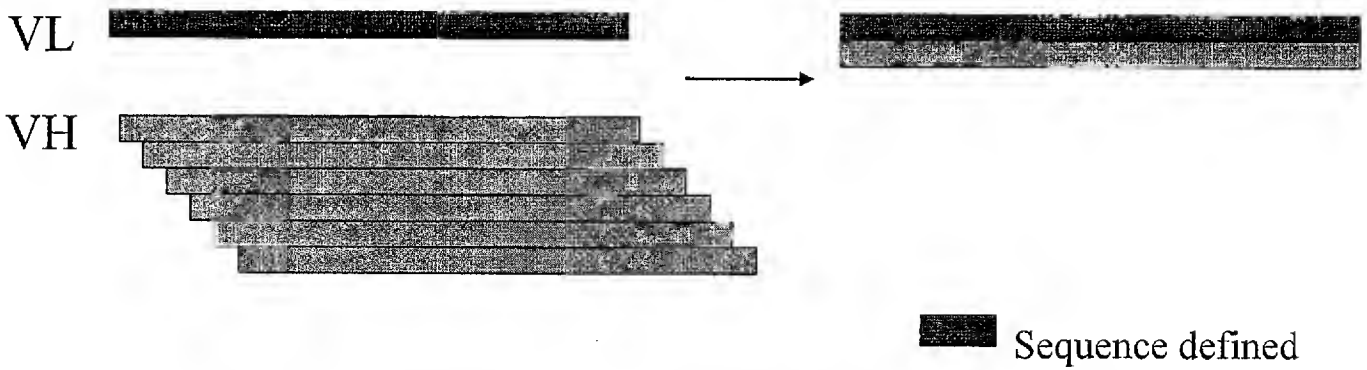


Specification

- Discloses antigen X from human tissue.
- Discloses antigen X is over-expressed in cancer tissue vs. normal tissue.
- The instant application produced an antibody that binds antigen X that contains a VH of SEQ ID NO:1 and a VL of SEQ ID NO:2, as well as explicitly disclosing humanized and chimaeric antibodies.
- The instant application provides examples of detection of cancer in human subjects with an antibody that binds antigen X.

State of the Prior Art

- There are several prior art[2] references that teach methods of producing antibodies that bind a specific antigen by using a specific VL (or VH) and screening a library of the complimentary variable domains.



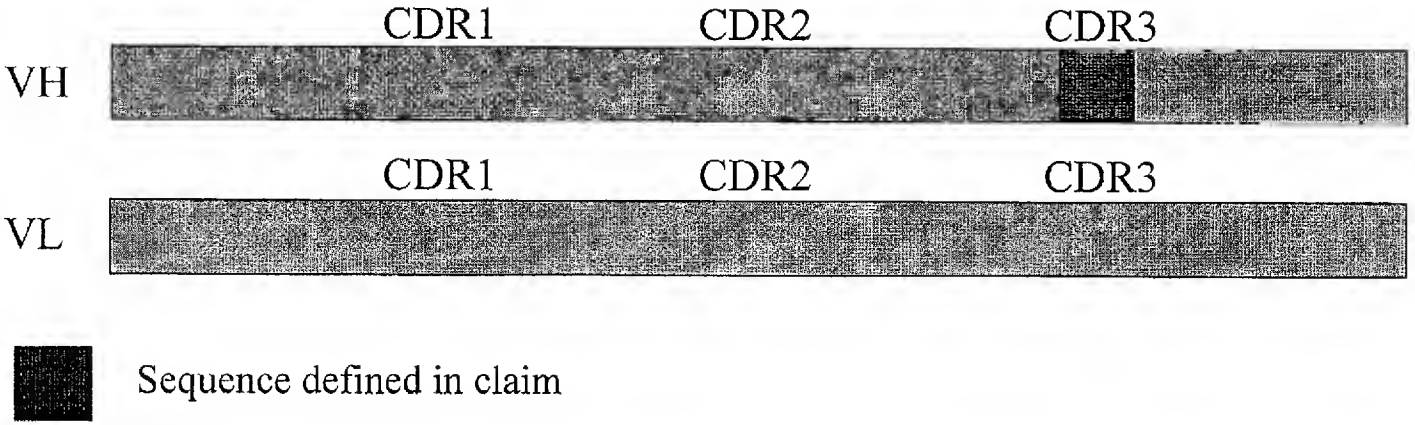
[2]Portolano et al., The Journal of Immunology (1993) 150:880-887
Clarkson et al., Nature (1991) 352:624-628

Analysis

- In light of the prior art disclosing methods of obtaining antibodies that bind an antigen by screening complementary variable domain libraries, the specification's disclosure of an antibody that binds a specific antigen comprising a defined VH or VL sequence would provide enough structure for one skilled in the art to practice the invention.
- Therefore, claims directed to an antibody that binds a specific antigen and comprises a defined VH or VL sequence meet the requirements under 35 U.S.C. 112, first paragraph, for enablement.

Example 3

- Claim: An isolated antibody that binds to human antigen X, said antibody comprises a heavy chain variable domain and a light chain variable domain, said heavy chain variable domain comprises the CDR3 in SEQ ID NO:1 (VH).



Specification

- Produced a series of antibodies that bind antigen X and the antibodies were not random combinations of VH and, i.e., VL they had specific VH domains paired with specific VL domains.
- The VH domains are highly homologous to each other and share not only CDR3, but also were nearly identical in framework regions (3-6/124 residues) as well as CDR1 (3/5)[1] and CDR2 (6/16)[1] regions.

| ▌indicates region where residues differ

[1] indicates residues that are identical out of number of residues in the CDR

Specification (cont.)

- Analysis of the VL sequences of these antibodies reveals that these domains are highly homologous to each other. The framework regions are nearly identical and the VL domains are identical in CDR1 and CDR2 regions. The CDR3 (8/10)[1] regions are highly homologous to each other.
- The instant application suggests that it was well established in the art at the time the invention was made that the CDR3 region alone can determine the specificity of the antibody.

[1] indicates residues that are identical out of number of residues in the CDR

State of the Prior Art

- Prior art for obtaining an antibody with only CDR3 of the VH defined:

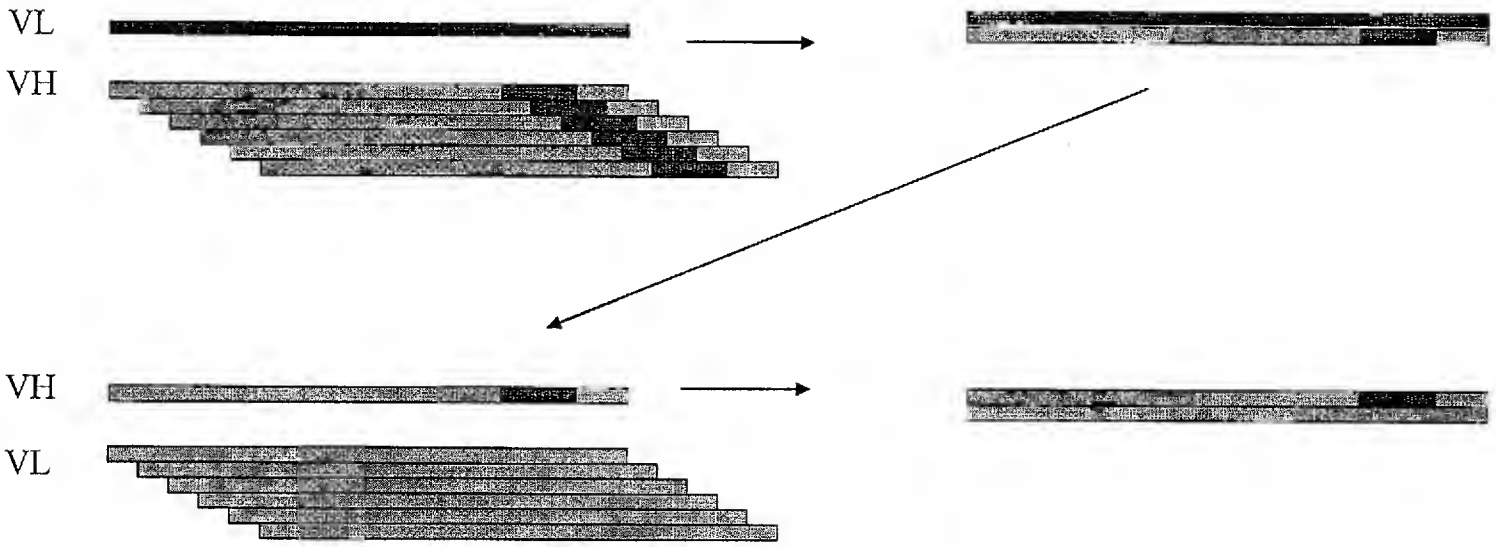
Klimka et al., British Journal of Cancer (2000) 83: 252-260: Klimka et al describe a screening process using a mouse VL and a human VH library with CDR3 and FR4 retained from the mouse VH. After obtaining antibodies, the VH was screened against a human VL library to obtain antibodies that bound antigen.

Beiboer et al., J. Mol. Biol. (2000) 296:833-849: Beiboer et al describe a screening process using the entire mouse heavy chain and a human light chain library. After obtaining antibodies, one VL was combined with a human VH library with the CDR3 of the mouse retained. Antibodies capable of binding antigen were obtained.

Rader et al., PNAS (1998) 95:8910-8915: Rader et al, describe a process similar to Beiboer et al above.

State of the Prior Art (cont.)

Method for screening



State of the Prior Art (cont.)

- The prior art methods for screening rely on a two step process where each step results in an antibody, however, each step requires one of the variable domains to be a defined sequence and the defined variable domain provides enough structure to obtain an antibody.
- The prior art methods do not result in an antibody solely by keeping CDR3 in the VH defined and randomizing the rest of the VH and VL domains.

State of the Prior Art (cont.)

- Prior art indicating the CDR3 region in the VH domain is important in antigen binding:

MacCallum et al., J. Mol. Biol. (1996) 262: 732-745: Analyzed many different antibodies for interaction with antigen and found that although CDR3 of the VH dominate the interaction, a number of residues outside the CDRs make antigen contacts and residues in the CDRs are important for backbone conformations.

Pascalis et al., the Journal of Immunology (2002) 169: 3076-3084: Grafting of CDRs onto a human framework required some residues in all 6 CDRs as well as specific frameworks.

Casset et al., BBRC (2003) 307, 198-205: Constructed a peptide mimetic of an anti-CD4 antibody binding site using 24 residues formed from residues from 5 of the CDRs. Casset et al., state that although CDR H3 is at the center of most antigen interactions, clearly other CDRs play an important role in recognition.

State of the Prior Art (cont.)

Vajdos et al., J. Mol. Biol. (2002) 320: 415-428: Antigen binding is primarily mediated by the CDRs but more highly conserved framework segments are mainly involved in supporting CDR loop conformations and, in some cases, framework residues also contact antigen.

Padlan et al., PNAS (1989) 86:5938-5942: Padlan et al describe the crystal structure of an antibody-lysozyme complex where all 6 CDRs contribute at least one residue to binding and one residue in the framework is also in contact with antigen.

Lamminmaki et al., JBC (2001) 276:36687-36694: Lamminmaki et al describe the crystal structure of an anti-estradiol antibody in complex with estradiol where, although CDRH3 plays a prominent role, all CDRs in the light chain make direct contact with antigen (even CDRL2, which is rarely directly involved in hapten binding).

State of the Prior Art (cont.)

- The prior art indicated that, in some instances, the CDR3 region is important. However, this region is not solely responsible for binding. The conformation of other CDRs, as well as framework residues influence binding.

State of the Prior Art (cont.)

- Transfer of only CDR3 in the VH and retention of antigen binding.

Barbas et al., PNAS (1995) 92: 2529-2533: Transferred the CDR3 of the VH of three anti-DNA antibody to an anti-tetanus toxoid antibody and retained DNA binding in 2/3 antibodies.

It was known in the art that antibodies that bind dsDNA can be generated by reconstruction of the CDR3 in the heavy chain of an antibody as well as transplantation of a 17 amino acid alpha-helical DNA binding domain into CDR3 of the heavy chain[3].

[3]McLane et al., PNAS (1995) 92:5214-5218,
Barbas et al., J. Am. Chem. Soc. (1994) 116:2161-2162

Analysis

- The claim is broadly drawn to any antibody that binds antigen X and comprises a heavy chain variable region comprising CDR3 in SEQ ID NO:1.
- The specification discloses antibodies with highly homologous VH and VL domains and identical VH CDR3 regions.
- The specification does not disclose that CDR3 of the VH alone can be transferred to just any framework and paired with just any VL and retain antigen binding.

Analysis (cont.)

- The specification does not provide any examples to support that CDR3 of the VH or VL is solely responsible for antigen binding.
- The prior art does not show screening for antibodies by just defining CDR3. The methods rely on using an entire VH or VL and screening random complimentary chains.
- The prior art does not show that a CDR3 is universally solely responsible for antigen binding.

Analysis (cont.)

- The prior art does not support a definition of an antibody structure solely by defining the CDR3 sequence of a VH or VL.
- Based on this analysis a claim to an isolated antibody that binds to human antigen X, said antibody comprises a heavy chain variable domain and a light chain variable domain, said heavy chain variable domain comprises the CDR3 in SEQ ID NO:1, does not meet the requirements of 35 U.S.C. 112, first paragraph, for enablement.

Prior Art

Antibodies

Example 3

- An isolated antibody which specifically binds to a polypeptide comprising SEQ ID NO: 1.

The Specification

- Discloses an isolated full length polypeptide comprising SEQ ID NO: 1.
- Discloses an antibody raised to the full length polypeptide.

Prior Art

- Reference Y teaches a protein that is 99% identical to SEQ ID NO: 1 over its full length.
- Reference Y also teaches an antibody that was raised to and specifically binds said protein of the art.

Rejection under 35 U.S.C. 102

- The specification does not define the term "specifically binds" and in light of the art accepted meanings given previously, the phrase is given its broadest reasonable interpretation and the phrase defines the act of an antibody binding to its antigenic determinant/epitope.
- The term "specifically" in this instance, absent a clear definition in the specification, is not interpreted to mean "exclusivity".
- Antibody binding to shared or similar epitopes on different antigens is known as cross-reactivity.
- The antigen of the art is highly related to the antigen used to raise the instantly claimed antibody, indeed, it is nearly identical.
- The antibody of prior art reference Y would support a rejection under 35 U.S.C. 102 of the claimed antibody because 99% identity is substantial evidence of cross-reactivity.

Example 4

- An isolated antibody which binds a fusion protein comprising SEQ ID NO: 1.

The Specification

- Discloses an isolated full length polypeptide comprising SEQ ID NO: 1.
- Discloses an antibody raised to the full length polypeptide.
- Discloses fusion proteins comprising SEQ ID NO: 1 and heterologous polypeptides selected from HIS tags and BSA.

Prior Art

- Reference X teaches antibodies which bind HIS tags for use in protein purification.

Conclusion

- The claim would be rejected under 35 U.S.C. 102 over the prior art reference X antibodies which would bind the instantly claimed fusion protein due to their ability to bind the HIS tags individually.

Patenting Antibodies

Questions?